Review

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The association between study characteristics and outcome in the relation between job stress and cardiovascular disease – a multilevel meta-regression analysis

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Objectives Studies about job strain and cardiovascular disease (CVD) have yielded inconsistent results, which hinders making a firm conclusion about the association. Inconsistent findings may be the result of methodological differences. If the relative CVD risk is influenced by methodological differences, these differences should be explored in more detail in future research to clarify which methodological characteristics are inherent to obtain the most accurate estimate between job strain and CVD risk. By assessing how study characteristics are associated with the outcome, we take the first step in unraveling this association. In this review, we explore the following research question: are study characteristics associated with the size of the reported relative CVD risk?

Methods A systematic literature search yielded 71 studies about job stress, assessed with the demand–control model, and CVD. Traditional meta-regression was extended enabling the use of correlated data to quantify heterogeneity within and between studies.

Results Compared to studies that use the original Job Content Questionnaire (JCQ), studies in which a more deviant form of the JCQ was used yielded, on average, 43% higher estimates. Studies conducted in the USA yielded about 26% lower estimates compared to studies conducted in Scandinavian countries.

Conclusions Several study characteristics are associated with the size of the reported relative CVD risk. Many of these study features are related to the validity of the exposure and outcome assessment and are inherent to obtain an accurate estimate between work stress and CVD risk. More research is needed to clarify why these study features impact the average relative CVD risk.

Key terms coronary heart disease; decision latitude; heterogeneity; job demand; job strain; meta-analysis; psychosocial factor; review; stroke; systematic review; work stress.

Cardiovascular disease (CVD) has a high prevalence in Western countries and many risk factors for developing CVD have been identified. Besides the traditional risk factors such as hypertension, diabetes, and smoking, work stress is also considered as a risk factor. Work stress has most often been operationalized with the demand–control model as job strain, which is the specific combination of high job demands and low decision latitude (1). Karasek hypothesized that employees who are exposed to job strain are at greatest risk for CVD (2). Job strain may increase CVD risk through direct activation of neuroendocrine responses leading to wear and tear of the cardiovascular system by initializing atherosclerosis and ultimately leading to CVD or ‚indirectly, through negatively affecting lifestyle factors, such as increasing smoking frequency and body mass index (3, 4).

The association between job strain and CVD has been investigated since the introduction of the demand–control model, but this association is highly debated due to conflicting results since consistency of the results is one of the criteria for establishing a causal associa-

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tion (5). Methodological differences between the studies might contribute to these conflicting results and it remains unclear whether an elevated risk is only found in studies with poor methodological quality, in studies that use a specific outcome or exposure assessment, or in studies with specific populations. Especially in studies where exposure and outcome are measured with self-reported data, overestimated associations are expected (6).

Studies that have focused on the association between job strain and CVD risk differ amongst others in the exposure assessment. Although exposure is operationalized according to the demand–control model, studies differ in whether they investigate job strain in relation to CVD, or whether they investigate demands or decision latitude separately. Some of these studies found an increased CVD risk associated with high demands (7–10) or low decision latitude (11–14), while job strain is hypothesized to be most harmful. Furthermore, exposure is most often assessed with a variety of slightly different questionnaires. Besides differences in exposure assessment (15), these studies also differ in their design, categorization of the exposure, populations, and CVD assessment.

While heterogeneity in results can be considered as problematic in scientific literature (16, 17), when the aim is to obtain a summary estimate for the effect of the risk factor of interest, some studies have recognized the potential of exploring the heterogeneity and investigated which study characteristics are associated with the study outcome (18–26). These types of studies have not been performed yet in occupational health research, specifically not in the field of job strain and CVD research where conflicting results prevail and an assessment of which study characteristics are associated with the reported CVD risk would be of value.

Clarifying how study characteristics influence the relative CVD risk is important for future research as it could lead to insight into what causes the differences. Therefore, we formulated the research question: what is the association between study characteristics and the reported effect size in studies about job strain and CVD? By exploring this research question, we aim to assess whether there is an association between study characteristics and the relative CVD risk. This in turn could lead to new hypotheses about the possible reasons for these expected differences. If these hypotheses are explored in future research, this can clarify which methodological characteristics are inherent to obtain the most accurate estimate between job strain and CVD risk. For this study, we used a multilevel meta-regression technique, which enables the use of multiple results from a study, exploiting it to its full potential since both the within- and between-study heterogeneity are used.

Methods

A literature search was performed during January–February of 2009 in the following databases: Pubmed, Web of Science, PsychInfo, and Embase. We used text words for exposure ("job strain", "job control", "decision latitude, "decision authority", "job demands", "job stress", "psychosocial work environment", "work stress", "occupational stress", "psychosocial risk factors", "effort–reward imbalance",[1] "psychosocial work characteristics", and "job characteristics"). For CVD, we used the MeSh term "cardiovascular disease" and the freetext words: "heart disease", "angina pectoris", "stroke", "coronary events", and "myocardial infarction". No restrictions for language or time period were used. In addition, we checked the reference lists from two reviews (15, 27) and Web of Science was searched using the "cited reference search". This was carried out for the studies of Kivimaki et al (28) and Theorell et al (29). The cited reference search yielded a list of articles that have cited these two studies. This list of articles was screened for not-yet-identified studies. Dissertation abstracts and meeting abstracts were also gathered and, when considered as potentially relevant, we tried to retrieve the fulltext article or thesis.

Selection of studies

Studies were eligible if they investigated the association between job strain or its components (job demands, decision latitude) and a manifest form of CVD. Furthermore, the results had to be presented with an association measure and accompanying confidence intervals. If these were not presented, at least data had to be presented that could be used to calculate an association measure. No other inclusion criteria were used, as the aim of this study was to include heterogeneous studies. Studies were excluded if they did not fulfill the inclusion criteria or for reasons presented in figure 1.

Data extraction

Multiple studies based on the same population were included if they differed in certain study characteristics (eg, length of follow-up duration) and were considered to be correlated.

Multiple results from one study were extracted and these results were considered to be correlated. Results stratified according to gender or age groups within one study were regarded as uncorrelated. The study characteristics that we thought were associated with the CVD risk were extracted and categorized into groups.

[1] ERI was included in the search strategy (although we do not use the results) because initially we planned to include this model as well.

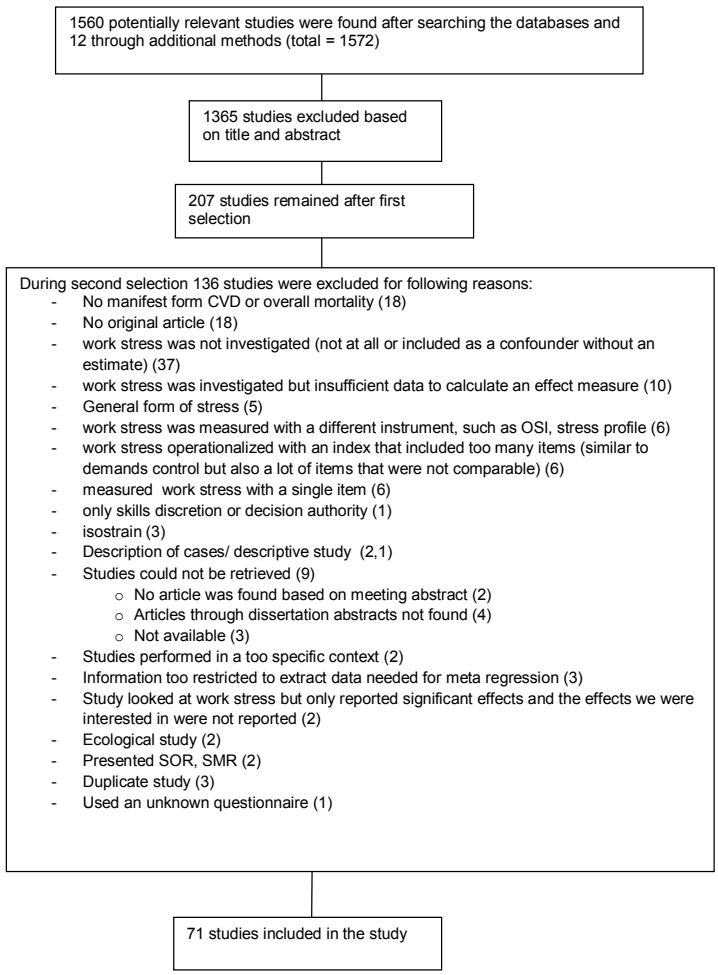

Figure 1. Flow chart of exclusion criteria.

Within these categories one category was the reference category (table 1). The categorization of most of these characteristics is unambiguous, however, outcome assessment, type of exposure questionnaires, adjustment for confounders in the individual studies, exposure levels, and quality score need more clarification, which can be found in the Appendix point A. For this study, cardiovascular subgroups (stroke, myocardial infarction, ischemic heart disease, both morbidity, and mortality) were grouped together, since the main underlying pathway is atherosclerosis (30).

Quality assessment of the studies

The quality of the studies was assessed by the first reviewer using the following items: selection bias, information bias, selective dropout, recall bias, valid exposure assessment, valid outcome measurement, dealing with confounders, and dealing with prevalent CVD cases at baseline or gathering information about disease history in controls. The score per item ranged from 0–5, with 0 denoting low risk of bias and 5 meaning high risk of bias. The various items were then evaluated for their importance (based upon the judgment of the reviewer) when assigning an overall score, and the quality of the studies were classified as "very poor", "poor", "moderate", "high", and "very high".

Statistical analysis

The model used for the analyses is an elaboration of the random-effects model described by Houwelingen et al (31), see Appendix point B. In the individual studies, the association between job strain and CVD is expressed with an odds ratio (OR), hazard ratio (HR) or RR. In this study, the dependent variable (y) is a summary statistic of the association measures presented in the individual studies. CVD is considered as a rare disease, and therefore OR and RR can be interpreted as being similar.

The intercept-only model is equal to the overall (pooled) estimate of the relative CVD risk when exposed to job strain (or one of its components, namely, low decision latitude or high job demands). To examine the influence of study features on the estimate, the model was

Table 1. Univariate associations between study characteristics and the reported relative cardiovascular disease (CVD) risk. [AMI=acute myocardial infarction; IHD=ischemic heart disease; JCQ=job content questionnaire; JEM=job exposure matrix; NA=not available; pop=population; ROR=ratio of the odds ratio; 95% CI=95% confidence interval.]

Characteristic	Job strain				Job demands				Decision latitude			
	N [a]	N [b]	ROR [c]	95% CI	N [a]	N [b]	ROR [c]	95% CI	N [a]	N [b]	ROR [c]	95% CI
Design												
Case–control	22	10	1.06	0.79–1.40	17	8	0.89	0.72–1.11	29	8	0.89	0.93–1.38
Cross sectional	20	7	1.08	0.79–1.49	16	6	1.05	0.86–1.28	19	7	1.02	0.87–1.20
Nested case–control	1	1	3.19	0.78–13.07	7	2	1.02	0.64–1.22	6	1	1.51	0.92–2.48
Cohort (reference)	83	17	1.00	..	84	23	1.00	..	123	26	1.00	..
Follow up duration (months)												
12–73	11	4	0.90	0.59–1.38	26	8	1.41	1.12–1.80	44	9	1.04	0.86–1.28
73–132	45	8	1.17	1.03–1.35	8	5	0.96	0.77–1.17	8	5	1.10	0.87–1.42
NA [d]	42	8	1.06	0.84–1.36	33	12	1.00	0.85–1.19	48	13	1.09	0.92–1.30
>134 (reference)	8	17	1.00	..	57	14	1.00	..	77	15	1.00	..
Gender sample												
Only women	24	6	0.77	0.56–1.05	43	10	0.95	0.79–1.14	54	11	1.15	0.99–1.33
Women and men	35	10	0.92	0.80–1.05	16	8	1.03	0.83–1.30	26	8	1.04	0.84–1.28
Only men (reference)	67	20	1.00	..	65	20	1.00	..	97	22	1.00	..
Maximum age limit of sample (years)												
65	89	26	1.12	0.80–1.55	59	23	1.15	0.97–1.39	97	27	0.92	0.77–1.12
>65	10	5	1.06	0.75–1.51	26	8	0.98	0.81–1.19	23	7	0.90	0.70–1.16
Unknown [e]	6	2	0.83	0.54–1.27	5	3	1.54	1.08–2.18	11	2	1.62	0.91–2.36
56 (reference)	21	5	1.00	..	34	5	1.00	..	46	6	1.00	..
Sample selection												
Occupation based	33	6	0.87	0.64–1.15	42	8	1.14	0.93–1.38	49	7	0.92	0.74–1.14
Single occupation	5	1	0.44	0.61–0.84	4	1	1.10	0.70–1.77	4	1	0.79	0.47–1.34
NA [f]	2	1	1.09	0.57–2.12	2	1	1.44	0.93–2.25	2	1	0.88	0.53–1.43
Pop-based (reference)	86	27	1.00	..	76	28	1.00	..	122	31	1.00	..
Association measure												
Prevalence ratio	1	1	1.21	0.68–2.14	0	0	.	..	0	0	.	..
Relative risk	6	2	0.55	0.42–0.72	7	3	1.20	0.93–1.54	27	6	0.94	0.79–1.12
Hazard ratio	70	16	0.89	0.75–1.08	75	20	1.06	0.90–1.26	58	20	0.88	0.75–1.20
Odds ratio (reference)	49	18	1.00	..	42	16	1.00	–	92	16	1.00	..
Measurement of CVD												
Questionnaire, doctor confirmed	6	2	1.22	0.77–1.95	5	2	1.01	0.73–1.39	5	2	0.89	0.62–1.25
Questionnaire, unknown/not doctor confirmed	10	3	1.35	0.88–2.14	12	5	1.11	0.91–1.35	15	6	1.05	0.87–1.25
Combination of self reported	0	0	.	..	1	1	1.19	0.88–1.60	1	1	0.92	0.64–1.35
Diagnostics (reference)	110	30	1.00	..	106	33	1.00	..	156	35	1.00	..
Exposure level												
>Median versus <median			.	..			1.10	0.99–1.21			1.18	1.08–1.29
Job strain												
High strain versus rest [g]	18	18	0.91	0.97–1.25			.	..			.	..
High strain versus rest [h]	17	17	1.00	0.73–1.35			.	..			–	..
High strain versus low strain [i] (reference)	19	19	1.00	..			.	..			–	..
Type of CVD												
Only morbidity	59	22	0.94	0.80–1.10	43	18	1.07	0.86–1.34	48	18	0.97	0.83–1.14
Morbidity and mortality	52	18	0.92	0.85–1.07	67	19	1.11	0.89–1.40	82	19	0.94	0.79–1.12
Mortality (reference)	15	5	1.00	..	14	5	1.00	..	47	8	1.00	..
CVD subgroup												
Stroke	26	6	1.17	0.99–1.42	9	4	0.94	0.76–1.16	30	6	0.97	0.84–1.14
Stroke and other CVD	16	5	1.01	0.87–1.19	28	8	1.00	0.81–1.23	38	8	0.96	0.78–1.19
CVD without stroke (reference)	84	29	1.00	..	87	29	1.00	..	109	30	1.00	..
CVD subgroup												
IHD	74	26	0.87	0.72–1.05	79	26	1.08	0.87–1.36	101	27	1.05	1.02–1.23
IHD and other CVD	26	9	0.83	0.69–0.99	36	12	1.04	0.87–1.25	46	12	0.98	0.81–1.17
CVD without IHD (reference)	26	6	1.00	..	9	4	1.00	..	30	6	1.00	..

Continued

Table 1. Continued

Characteristic	Job strain				Job demands				Decision latitude			
	N [a]	N [b]	ROR [c]	95% CI	N [a]	N [b]	ROR [c]	95% CI	N [a]	N [b]	ROR [c]	95% CI
CVD subgroup												
AMI	30	15	0.81	0.69–0.96	22	12	0.94	0.76–1.15	33	12	0.99	0.90–1.38
AMI and other CVD	59	17	0.83	0.65–0.90	84	23	1.04	0.87–1.25	105	24	0.90	0.86–1.32
CVD without AMI (reference)	37	10	1.00	..	18	8	1.00	..	39	10	1.00	..
Type of questionnaire												
Different [j]	42	14	1.63	1.22–2.23	58	20	0.97	0.80–1.19	59	18	1.11	0.90–1.38
JCQ-like	61	15	1.30	0.99–1.72	46	10	0.91	0.73–1.14	98	15	1.07	0.86–1.32
Original JCQ (reference)	23	7	1.00	..	20	8	1.00	..	20	8	1.00	..
Type of answer scales												
Frequency [k]	38	13	1.17	0.92–1.49	60	14	0.92	0.79–1.07	108	18	1.13	0.95–1.34
Strain	16	2	1.39	0.86–2.20	4	1	1.04	0.70–1.50	12	1	0.76	0.47–1.22
Dichotomous	14	5	1.84	1.19–2.77	19	8	1.36	1.08–1.74	13	6	1.17	0.87–1.57
Unknown [l]	8	2	2.14	1.03–4.39	4	4	0.93	0.73–1.19	7	3	1.04	0.80–1.34
Opinion (reference)	50	14	1.00	..	37	13	1.00	..	37	13	1.00	..
Type of exposure												
JEM	11	6	0.89	0.68–1.16	20	8	0.81	0.70–0.92	58	12	1.07	0.94–1.21
Questionnaire (reference)	115	30	1.00	..	104	30	1.00	..	119	30	1.00	..
Number of exposure assessments												
>1	4	3	1.08	0.93–1.26	2	2	0.89	0.60–1.19	6	3	1.07	0.90–1.30
1 (reference)	122	33	1.00	..	122	36	1.00	..	171	38	1.00	..
Study quality												
Good	63	12	1.07	0.96–1.19	49	12	1.02	0.86–1.20	67	12	0.95	0.80–1.12
Poor (reference)	63	25	1.00	..	75	26	1.00	..	110	29	1.00	..
Publication year												
<1990	10	4	1.30	0.93–1.82	2	2	0.90	0.60–1.32	1	1	0.87	0.52–1.49
1990–2000	38	12	0.99	0.88–1.13	27	11	0.87	0.74–1.01	39	12	1.03	0.86–1.22
>2000 (reference)	78	22	1.00	..	95	25	1.00	..	137	27	1.00	..
Country of study												
West Europe (UK, The Netherlands, Germany, Belgium)	19	5	0.98	0.78–1.23	39	6	1.02	0.84–1.23	39	6	1.04	0.84–1.30
Japan	21	4	1.32	0.92–1.92	15	5	1.20	0.88–1.65	11	4	0.91	0.59–1.39
USA (Hawaii)	15	5	0.62	0.50–0.77	11	6	0.87	0.73–1.04	15	7	0.88	0.72–1.08
Other (Turkey, Lithuania, Czech Republic)	5	3	0.67	0.45–1.00	9	3	0.65	0.47–0.90	13	3	0.88	0.63–1.23
Scandinavia (reference)	66	18	1.00	..	50	18	1.00	..	99	20	1.00	..
Time of study												
1950-1970	24	8	0.84	0.55–1.30	25	10	0.83	0.68–0.99	34	9	0.90	0.69–1.15
1990-2000	75	22	0.91	0.61–1.36	65	21	0.98	0.82–1.17	112	25	0.91	0.28–3.03
Unknown [m]	2	1	1.19	1.49–2.92	1	1	0.91	0.27–3.06	1	1	0.91	0.72–1.14
1980–1989 (reference)	25	4	1.00	..	33	6	1.00	..	30	5	1.00	..

[a] Number of results.
[b] Number of studies.
[c] Expressed as the relative CVD risk in studies with a specific characteristic relative to the relative CVD risk in studies with a reference characteristic.
[d] Case–control studies and cross sectional studies.
[e] One study did not specify the age limit of the sample.
[f] Multicenter study in which different samples were used: 3 centers had an occupation-based sample and 3 centers had a population-based sample.
[g] High strain = demands above median value and decision latitude below median value versus the other three quadrants.
[h] High strain= alternative formulations than based on median value.
[i] High strain= demands above median value and decision latitude below median value versus low strain.
[j] Contains one study that uses the Karasek method (based on occupation) for assigning exposed/not exposed status.
[k] 3 studies use a work organization matrix, in which the demands scale has yes/no answers scales and decision latitude scale has frequency answer scales.
[l] 4 studies do not report which scales they used.
[m] 4 studies did not report the time period.

extended to contain one or multiple study characteristics (X). The model coefficients (ie, betas) indicate the extent to which a study characteristic influences the estimate and gives the ratio for the average OR in studies with a certain study characteristic relative to the average relative CVD risk in studies with a reference study characteristic. This is expressed as the ratio of OR (ROR), as also used in the study by Schulz et al (32).

A ROR of >1 indicates that studies in the referent group yield on average lower estimates and a ROR of <1 indicates that studies in the referent group yield on average higher estimates. For example, a ROR of 1.30 means that the estimate in studies with study feature X were on average 30% higher than studies with the reference study feature. A ROR close to 1 indicates that the study feature does not impact the estimate.

The multilevel character of the model stems from the fact that we allowed a study to contribute multiple results (effects) to the analysis, resulting in two levels of heterogeneity: within- and between-study heterogeneity. The way we accounted for such correlated data, is described in Appendix point B. For both effects (true and observed), a constant correlation was assumed. The SAS PROC MIXED procedure (SAS Institute, Cary, NC, USA) was used to perform the analyses using restricted maximum likelihood estimation to estimate the model parameters.

Model construction

The univariate associations (table 1) were examined and used to identify the most relevant study characteristics to be associated with the outcome (based on the magnitude of the association and, to a lesser extent, the width of the confidence interval). These were included in the multivariate model. If study features were highly correlated (eg, type of association measure and design), the variable that was most strongly associated with the relative CVD risk (mainly based on the magnitude of the association and to a lesser extent the width of the confidence interval) was included. This procedure was followed for all study features, except for the study feature "correction for confounders within a study". For this characteristic a different procedure was followed, which is described in Appendix point C.

Sub-analysis

Two sub-analyses were performed: one was performed in a selection of studies that used self-reported exposure and self-reported outcome. The overall pooled relative CVD risk was calculated. The second sub-analysis was performed in studies that used self-reported exposure and a more objective outcome (medically diagnosed CVD). Again, the pooled relative CVD risk was calculated and the effect of study features on the relative CVD risk was examined. The results of these sub-analyses were compared with the results that were based on all studies to examine whether conducting the analyses in a specific type of studies changed the impact of study features on the relative CVD risk.

Publication bias

The presence of publication bias was examined for studies examining the association between job strain and CVD by means of visual inspection of the funnel plot and statistical testing with the Egger test (33).

Results

The broad search strategy yielded 1560 articles, of which 71 were included in the meta-regression analysis (see figure 1). Of these studies, 46 studies were about job strain (2, 8–10, 28, 29, 34–73), 37 studies about job demands (2, 7–10, 12, 28, 34, 35, 37, 40–42, 45, 47–49, 54–56, 58, 61–63, 65, 69, 70, 73–82), and 43 studies about decision latitude (8–12, 14, 28, 29, 34, 35, 37, 38, 40–42, 45, 47–49, 54–56, 58, 61–63, 65, 69, 70, 73, 75, 76, 78–88).

The intercept-only model yielded an overall pooled relative CVD risk of 1.30 [95% confidence interval (95% CI) 1.14–1.46] for employees who are exposed to job strain compared to those who are not. The pooled relative CVD risk was 1.05 (95% CI 0.97–1.14) for employees exposed to high or intermediate job demands and 1.14 (95% CI 1.05–1.23) for those exposed to low or intermediate decision latitude compared to those with high decision latitude.

Univariate associations

In table 1, the univariate associations are given between the various study characteristics and the relative CVD risk. Studies rated as being of good quality yielded similar relative CVD risk estimates as those from poor quality studies; ROR were 1.07 (95% CI 0.96–1.19), 1.02 (95% CI 0.86–1.20), and 0.95 (95% CI 0.80–1.12) for studies about job strain, demands, and decision latitude, respectively. The ROR represent the ratio for the average OR in good quality studies relative to the average relative CVD risk in poor quality studies, which did not differ from each other.

Multivariate associations for job strain, job demands, and decision latitude

The country in which the studies are performed influenced the estimate. Studies performed in Japan yielded on average higher estimates compared to studies

performed in Scandinavia. The ROR was 1.30 (95% CI 0.93–1.84), which means that the estimate in Japanese studies was on average 30% higher than in Scandinavian studies, although not statistically significant. Studies performed in the USA and "other" countries yielded, on average, 39% lower estimates compared to Scandinavian studies (see table 2).

The type of exposure questionnaire was associated with the estimate. Studies that used a more deviant form of the Job Content Questionnaire (JCQ) to assess job strain yielded, on average, 43% higher estimates (ROR 1.43, 95% CI 1.07–1.92) than studies that used the original JCQ. Also the type of outcome assessment influenced the estimate, where studies that used questionnaires to assess CVD yielded 39% higher estimates compared to studies that used medically confirmed data on CVD (ROR 1.39, 95% CI 0.97–1.97).

For the association between job demands and CVD, again the country in which the study was performed influenced the estimate. Studies performed in countries categorized as "other" yielded a 43% lower estimate than studies performed in Scandinavia, see table 7 (ROR 0.57, 95% CI 0.43–0.76). Also the type of exposure assessment influenced the estimate, where studies that used a JEM to assess exposure to job demands yielded a 19% lower estimate than studies using questionnaires to assess job demands (ROR 0.81, 95% CI 0.71–0.91), see table 2.

Statistical adjustment for potential confounders within studies was associated with the estimate. In studies examining the association between job strain and CVD, compared to studies that do not adjust for confounders, adjustment for risk factors influenced the estimate in the following ways: (i) adjustment for age yielded 23% higher estimates than studies that do not adjust for age (ROR 1.23, 95% CI 1.08–1.42); (ii) adjustment for gender yielded a 13% lower estimate (ROR 0.87, 95% CI 0.77–0.98); (iii) adjustment for body mass index (BMI) yielded an 11% lower estimate (ROR 0.89, 95% CI 0.82–0.97).

In studies investigating the association between decision latitude and CVD, adjustment for socioeconomic status yielded, on average, a 12% lower estimate (ROR 0.88, 95% CI 0.83–0.93) compared to studies that do not adjust for socioeconomic status.

Sub-analysis

Studies that used self-reported exposure and outcome yielded an overall pooled relative CVD risk of 1.56 (95% CI 1.36–1.78), while studies that used medically diagnosed outcomes yielded an overall pooled relative CVD risk of 1.31 (95% CI 1.10–1.54). The impact of the study characteristics on the relative CVD risk in the sub-analysis conducted in studies that used medically diagnosed outcomes was similar to the impact of the study characteristics on the CVD risk in all studies.

Publication bias

Visual inspection of the funnel plot indicates the presence of bias since smaller studies (less precision) showing no effects are missing. The Egger test confirms the finding of bias (P=0.004) (data not shown).

Discussion

In this review, we explored the association between study characteristics and outcome in studies examining the relation between job strain and CVD using an extended form of meta-regression. We found that several study features are associated with the size of the relative CVD risk. The main findings that we consider worthwhile to explore in future research or which require some additional indepth discussion are described below. Furthermore, we discuss the strengths and limitations of this study that are important for the proper interpretation of the results.

Study features that are associated with the size of the CVD risk

To our knowledge, there are no studies that have assessed the association between study features and outcome in the field of job strain and CVD. Kivimaki et al (89) performed a meta-analysis on cohort studies exploring the association between job strain and CVD and reported a pooled estimate of 1.43 (95% CI 1.15–1.84), which is similar to the overall pooled estimate found in the present review.

We present results for job strain, job demands, and decision latitude. In the majority of studies we examined, job strain was analyzed as a quadrant term (the combination of having a job demands score above the median and having a decision latitude score below the median) or as an alternative combination term. As has been mentioned by Mikkelsen et al (90), this type of job strain measure does not test an interaction effect between decision latitude and job demands and an effect reported in these studies may be due to an effect of only one of these two factors.

In this review, studies that used different endpoints were grouped together. The main underlying cause of myocardial infarction, angina pectoris, and stroke (ischemic type) is atherosclerosis (91, 92), which is one of the hypothesized mechanism through which exposure to job strain could lead to CVD (15, 93). Furthermore, it is not uncommon for studies that have examined the association between job strain and CVD to combine several endpoints into one outcome (28, 39, 81, 87). The only point of concern might be within the stroke group, where the pathway between hemorrhagic strokes and ischemic

Table 2. Results from the multivariate model [a] for the association between study characteristics and reported relative cardiovascular disease (CVD) risk, according to exposure (job strain, job demands, decision latitude). [BMI=body mass index; JCQ=job content questionnaire; ROR=ratio of the odds ratio; SES=socioeconomic status; 95% CI=95% confidence interval.]

Characteristic	Categories	Job strain		Job demands		Decision latitude	
		ROR [b]	95% CI	ROR [b]	95% CI	ROR [b]	95% CI
Country of study	West Europe (UK, The Netherlands, Germany, Belgium)	1.09	0.84–1.43	0.94	0.81–1.07	.	..
	Japan	1.30	0.93–1.84	0.98	0.81–1.07	.	..
	USA (Hawaii)	0.74	0.59–0.93	0.98	0.84–1.17	.	..
	Other (Turkey, Lithuania, Czech Republic)	0.61	0.41–0.90	0.57	0.43–0.76	.	..
	Scandinavia (reference)	1.00	..	1.00	..	.	..
Type of questionnaire	Different	1.43	1.07–1.92	.	..	.	..
	JCQ-like	1.23	0.97–1.54	.	..	.	..
	Original JCQ (reference)	1.00		.	..	.	..
Measurement of CVD	Questionnaire, doctor confirmed	0.76	0.48–1.21	.	..	.	..
	Questionnaire, unknown/not doctor confirmed	1.39	0.97–1.97	.	..	.	..
	Diagnostics (reference)	1.00	..	.	..	.	..
Association measure	Prevalence ratio	1.55	0.84–2.83	.	..	.	..
	Relative risk	0.70	0.55–0.91	.	..	.	..
	Hazard ratio	1.06	0.89–1.26	.	..	.	..
	Odds ratio (reference)	1.00	..	.	..	.	..
Gender of sample	Only women	0.86	0.70–1.04	0.95	0.89–1.20	1.17	1.03–1.34
	Women and men	0.85	0.77–0.98	1.06	0.93–1.21	1.07	0.87–1.34
	Only men (reference)	1.00		1.00	..	1.00	..
Age	Adjustment yes	1.23	1.08–1.42	.	..	.	..
	Adjustment no (reference)	1.00		.	..	.	..
Gender	Adjustment yes	0.87	0.77–0.98	.	..	.	..
	Adjustment no (reference)	1.00		.	..	.	..
BMI	Adjustment yes	0.89	0.82–0.97	.	..	.	..
	Adjustment no (reference)	1.00	..	.	..	.	..
Age	Adjustment yes	.	..	0.87	0.72–1.04	.	..
	Adjustment no (reference)	.	..	1.00	..	.	..
Alcohol	Adjustment yes	.	..	1.27	1.03–1.55	.	..
	Adjustment no (reference)	.	..	1.00	..	.	..
SES	Adjustment yes	.	..	.	..	0.88	0.83–0.93
	Adjustment no (reference)	.	..	.	..	1.00	..
Type of exposure	Job exposure matrix (JEM)	.	..	0.81	0.71–0.91	.	..
	Questionnaire (reference)	.	..	1.00		.	..
Follow up duration	12–73	.	..	1.32	1.11–1.58	.	..
	73–132	.	..	0.96	0.83–1.11	.	..
	>134 (reference)	.	..	1.00	..	.	.
Exposure level	>Median versus <median	.	..	1.11	1.00–1.22	1.17	1.08–1.26
Type of answer scales	Frequency	.	..	1.04	0.90–1.22	.	..
	Strain	.	..	0.96	0.73–1.26	.	..
	Dichotomous	.	..	1.30	1.09–1.54	.	..
	Unknown	.	..	0.90	0.73–1.08	.	..
	Opinion (reference)	.	..	1.00	..	.	..
Max age limit of sample	65	.	..	.	..	0.90	0.76–1.05
	>65	.	..	.	..	0.83	0.66–1.04
	56 (reference)	.	..	.	..	1.00	
Design	Case–control	.	..	.	..	0.90	0.91–1.34
	Cross sectional	.	..	.	..	0.99	0.90–1.15
	Nested case–control	.	..	.	..	1.90	1.12–3.19
	Cohort (reference)	.	..	.	..	1.00	..

[a] The procedure for the selection of the variables into the multivariate model is described in the methods (model selection).
[b] Expressed as the relative CVD risk in studies with a specific characteristic relative to relative CVD risk in studies with a reference characteristic.

stroke differs. High blood pressure is more important in the former and atherosclerosis is more important in the latter (91, 92). Within the meta-regression analysis only three (55, 71, 88) of the five studies (55, 59, 71, 77, 88) that focused on stroke as an endpoint examined the effect of job strain (or one of the components) on different stroke subtypes, where results have been conflicting regarding the effect of job strain on different sub-types.

In the current study, no association was found between type of study design and the outcome. Initially, a more conservative estimate for the cohort studies was expected since information and recall bias are thought to give an overestimation of the association and are more likely to occur in cross sectional and case–control studies. However, the included cohort studies are also not free from bias. It is difficult to assess whether selective dropout has occurred during follow-up, and also not every cohort study has the availability of data about potential confounders and thus do not adjust for them. Furthermore, the majority of cohort studies use a single-time measurement for exposure and assume that exposure remains stable during follow-up, while little is known about the variability of exposure during follow-up and how this affects the reported association. Swaen et al (94), who investigated whether design was associated with a false positive finding in occupational cancer epidemiology, also did not find such an association.

In their previous review, Eller et al (15) pointed out that a large variation exists in the measurements of exposure. Our review shows that lower relative CVD risks are reported in studies that used a job exposure matrix (JEM) versus questionnaires to assess job demands. This is consistent with previously conducted studies (35, 63, 65, 70) and findings of reviews (15). The demands scale is considered to be the most subjective component of the job strain formulation (95), and assigning exposure status based on job title does not capture the perception differences among employees in the same job. This also raises the question whether the JCQ measures the work environment or the perceived work environment, which is crucial for prevention. The current study adds information by showing that also the type of questionnaire is related to the estimate, which raises the question: "what do these different instruments measure?" These findings underscore the importance of evaluating the validity of currently used exposure measures for assessing work stressors. The JCQ – and variations thereof – have never been tested as to whether they are indeed associated with work stress and assess the most important dimensions of the work environment; these are two basic properties of a measure to assess the psychosocial work environment accurately.

A valid exposure assessment is critical in properly establishing the relation between job strain and CVD (6, 96). Therefore, more research is needed to determine which specific factors in the work environment [such as type of job demands (97, 98)] measure the concept of job stress most appropriately and can be used to most accurately assess the association between job stress and CVD.

In this study, the country in which the study was performed was associated with the reported CVD estimate. Different job strain levels across countries could explain this. However, since exposure level is not given by absolute values but rather according to categories in the majority of the studies, this was not possible to examine. Only a few studies (99, 100) compared the absolute values of job strain between countries and did not find a difference in exposure level. Another explanation for these national differences is that items are given different meanings due to, for example, culture (15, 97, 101) or not perceiving job strain as a risk factor.

Furthermore, in this study we also found that studies using self-reported CVD as an outcome yielded, on average, higher relative CVD risks compared to studies that use medically diagnosed outcomes. This might indicate an overestimation of the association between job strain and CVD risk as employees exposed to high job strain might confuse job strain symptoms with cardiovascular symptoms (angina pectoris). Common method bias may also be an explanation (102), where the observed association in studies using self-reported outcome and exposure might be inflated due to bias. Negative affectivity has been suggested as a source of bias that can produce common method bias, since self-reports of individuals high in negative affectivity are likely to be biased in a negative direction, leading to over-reporting of job stressors and physical symptoms. The results of the subanalysis conducted in studies that used self-reported outcome and exposure suggest such an inflated association.

No association was found between study quality and average relative CVD risk, which was unexpected since the risk of bias is more substantial in poor than good quality studies. We expected that most forms of bias would yield an overestimation of the estimate, thus poor quality studies were hypothesized to yield a higher estimate than good quality ones. In this study, one reviewer performed the quality assessment. This is a disadvantage because quality rating is a rather subjective procedure. Moreover, the overall judgment was not simply based on counting the scored items but several items were weighted more than others in the assignment of an overall score. Furthermore, studies that were rated as "very good" and "good" were grouped together, as were the "moderate" and "poor" quality studies, which decreases the contrast in quality and could have led to an underestimation of the effect of study quality on the effect estimate.

Limitations and strengths of the study

Publication bias was present in this study, which could have led to an overestimation of the pooled estimate (103, 104). However, how publication bias could have

influenced the association between the study features and CVD risk is more difficult to predict because it depends on the distribution of the study features in relation to the size of the CVD risk in the non-published studies. It is unlikely that publication bias influenced our results for the majority of study features, since this would indicate that study features in the small studies showing no effects differ systematically from the study features in the larger studies and small studies that show an effect. Editors and reviewers tend to dislike negative studies and rejection is rather related to this than to study quality (105).

Furthermore, the correlation between the multiple results from the same sample had to be modeled since these are no longer independent. We assumed a constant correlation for multiple results within one study and that this was the same across all studies. While a constant correlation seems plausible for some results, for other results (such as those belonging to different CVD outcomes or exposure or different follow-up length) this seems less likely. Testing the possible implications of potentially violating this assumption was not feasible. However, we were able to test the impact of a change in the correlation of the between study differences. This showed that the correlation between the random effects had only a minor influence on the estimates; the direction and the magnitude of the effect remained the same.

The benefit of performing a meta-regression on correlated data is that multiple results reported by one study can be used to their full potential, increasing the prevalence of certain study characteristics. The other advantage is the availability of the within-study variation for some study characteristics. These results provide the most direct/valid estimates of the impact of the study characteristics because all the other study features in that study are held constant and a difference in effect size can therefore be assigned to that specific characteristic. Furthermore, using correlated data increased the study power.

The risk of false positive findings is present because of the multitude of study characteristics that were evaluated (106–108), and the risk of confounding is possible due to the combination of relative few studies and a multitude of study characteristics. However, the associations presented in this study are plausible and in line with results available from individual studies and reviews as described above. Furthermore, we were able to adjust the results for the most relevant study characteristics in the multivariate model and using a random effects model accounts for any unexplained residual heterogeneity.

Also, the sub-analysis performed in a selection of studies that only used medically diagnosed outcomes yielded similar estimates for the study features, as compared to the results based on all types of studies.

In conclusion, this review has shown that study features are associated with the estimate. With future research it should be examined why country, type of CVD assessment, type of exposure questionnaire, and the gender of the sample are related to the estimate. Most of these factors seem to be related to the validity of assessing the psychosocial work environment or outcome, which probably explains why the results in this field are so conflicting. If the measures used are not measuring what we intend to measure, the estimate is influenced by other factors. These issues need to be investigated and resolved (eg, initializing research in which the validity of measuring the psychosocial work environment is examined) so that the association between work stress and CVD can be more accurately assessed.

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